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Hematopoietic Stem Cell Transplantation Using Preimplantation Genetic Diagnosis and Human Leukocyte Antigen Typing for Human Leukocyte Antigen–Matched Sibling Donor: A Turkish Multicenter Study

Emin Kurekci [1,*], Alphan Küpesiz [2], Sema Anak [3], Gülyüz Öztürk [4], Orhan Gürsel [5], Serap Aksoylar [6], Talia Ileri [7], Barış Kuşkonmaz [8], İbrahim Eker [5], Mualla Cetin [8], Gülsün Tezcan Karasu [9], Zühre Kaya [10], Tunç Fışgın [11], Mehmet Ertem [7], Savaş Kansoy [6], Mehmet Akif Yeşilipek [12]

[1] *Department of Pediatric Hematology, Lösante Hospital Ankara, Ankara, Turkey*
[2] *Department of Pediatric Hematology and Oncology, Akdeniz University Medical Faculty, Antalya, Turkey*
[3] *Department of Pediatric Hematology and Oncology, İstanbul University Medical Faculty, Istanbul, Turkey*
[4] *Pediatric Bone Marrow Transplantation Unit, Medical Park Bahçelievler Hospital, Istanbul, Turkey*
[5] *Department of Pediatric Hematology, Gülhane Military Medical Academy and Medical Faculty, Ankara, Turkey*
[6] *Department of Pediatric Hematology and Oncology, Ege University Medical Faculty, Izmir, Turkey*
[7] *Department of Pediatric Hematology and Oncology, Ankara University Medical Faculty, Ankara, Turkey*
[8] *Department of Pediatric Hematology and Oncology, Hacettepe University Medical Faculty, Ankara, Turkey*
[9] *Bahçeşehir University Medical Faculty, Medical Park Göztepe Hospital, Istanbul, Turkey*
[10] *Department of Pediatric Hematology and Oncology, Gazi University Medical Faculty, Ankara, Turkey*
[11] *Bahçeşehir University Medical Faculty, Medical Park Bahçelievler Hospital, Istanbul, Turkey*
[12] *Turkish Pediatric Bone Marrow Transplantation Study Group. Bahçeşehir University Medical Faculty, Medical Park Göztepe Hospital, Istanbul, Turkey*

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A B S T R A C T

Preimplantation genetic diagnosis involves the diagnosis of a genetic disorder in embryos obtained through in vitro fertilization, selection of healthy embryos, and transfer of the embryos to the mother's uterus. Preimplantation genetic diagnosis has been used not only to avoid the risk of having an affected child, but it also offers, using HLA matching, preselection of potential HLA-genoidentical healthy donor progeny for an affected sibling who requires bone marrow transplantation. Here, we share the hematopoietic stem cell transplantation results of 52 patients with different benign and malign hematological or metabolic diseases or immunodeficiencies whose donors were siblings born with this technique in Turkey since 2008. The median age of the patients' at the time of the transplantation was 8 years (range, 3 to 16 years) and the median age of the donors was 2 years (range, .5 to 6 years). The most common indication for HSCT was thalassemia major (42 of all patients, 80%). The stem cell source in all of the transplantations was bone marrow. In 37 of the transplantations, umbilical cord blood of the same donor was also used. In 50 of the 52 patients, full engraftment was achieved with a mean of 4.6×10^6 CD 34^+ cells per kg of recipient weight. Ninety-six percent of the patients have been cured through hematopoietic stem cell transplantation without any complication. Primary engraftment failure was seen in only 2 patients with thalassemia major. All of the donors and the patients are alive with good health status. Preimplantation genetic diagnosis with HLA matching offers a life-saving chance for patients who need transplantation but lack an HLA genoidentical donor.

INTRODUCTION

Preimplantation genetic diagnosis (PGD) is a method for diagnosing genetic diseases in the early embryonic period so that implantation of affected embryos can be avoided and the potential need for termination of pregnancy is eliminated in families who have genetic diseases. The first application of

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* Correspondence and reprint requests: Emin Kurekci, MD, Department of Pediatric Hematology, Lösante Hospital, 06830 İncek-Gölbaşı, Ankara, Turkey.
E-mail address: ekurekci@gmail.com (E. Kurekci).

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PGD was in 2009 by Petrou, who reported that the biopsy of up to 2 cells from the 8-cell-stage embryo did not affect the development of the embryo to the blastocyst stage or the embryo metabolism [1]. PGD is also used with preimplantation HLA typing for treatment of affected siblings with genetic and acquired disorders who require HLA-matched stem cell transplantation [2]. The PGD and HLA-matching procedure is a form of in vitro fertilization (IVF) that requires a multiplex polymerase chain reaction amplification, in which the simultaneous analysis of gene mutations and HLA typing are done on a single blastomere. The first successful application of PGD combined with HLA typing was reported by Verlinsky et al. in 2001 [3] with the transplantation outcomes reported by Grewal et al. in 2004 [4] for a case of Fanconi anemia resulting in a successful tissue reconstitution after stem cell transplantation [3,4].

HLA typing without mutation analysis has also been used for acquired diseases, such as acute myeloid leukemia and acute lymphoid leukemia, which require allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-identical donor for the cure of the disease [5]. Because of limited availability of HLA-matched donors, even among family members, preimplantation HLA typing without mutation analysis appeared to be attractive for couples with children who have acquired diseases requiring HLA-matched bone marrow transplantation and do not have HLA-matched donor. It has been 15 years since the first successful application of PGD combined with HLA typing, and preimplantation HLA typing with or without mutation analysis has become 1 of the major pretreatment assessments for an increasing number of congenital and acquired diseases [6].

The present data include HSCT results of 52 patients in Turkey, who, since 2008, had benign or malign hematological diseases, metabolic diseases, or immunodeficiencies and whose donors were the siblings born via preimplantation HLA typing with or without mutation analysis. As far as we know, this is the largest case series on the subject performed to date in the literature and may, therefore, provide valuable information for clinical outcomes of the transplantations with donors born via this technique.

MATERIALS AND METHODS

Patient and Donor Characteristics

Between February 2008 and January 2014, 52 patients underwent 53 transplantations in 11 pediatric HSCT centers in Turkey with transplants from siblings born via preimplantation HLA typing with or without mutation analysis. One of the patient with thalassemia major (TM) had undergone a second transplantation from the same donor because of primary graft failure. The demographic characteristics of patients and donors are shown in Table 1.The median age of patients at the time of transplantation was 8 years (range, 3 to 16 years); 23 (44.2%) were female and 29 (55.8%) were male. One patient with TM and 1 patient with acute lymphoblastic leukemia had undergone transplantation from both of their twin siblings. Because of this, the total number of the donors was 54 and 28 of them (52.8%) were female and 26 of them (47.2%) were male. The most common indication for HSCT was TM (42 of all patients, 80%). Consent was obtained at PGD and HLA typing, at IVF cycle, at umbilical cord cryopreservation, and at the beginning of HSCT.

HSCT Characteristics

In all of the transplantations, bone marrow was used as the stem cell source. In 37 of the transplantations, umbilical cord blood of the same donor was also used. In all patients, except the 1 with TM who had undergone bone marrow transplantation twice, 1 bone marrow harvesting procedure was enough to collect the targeted total nucleated cell count. The 6 TM patients who were considered high risk according to classification proposed by Pesaro group were conditioned with Pesaro protocol 26 plus antithymocyte globulin. Of the 36 TM patients who were considered low risk, 34 were conditioned with regimens including busulfan and cyclophosphamide, while the remaining 2 were conditioned with regimens including treosulfan, thiotepa, and fludarabine. The conditioning regimens of the other patients are seen in Table 2. All patients were given different immunosuppressants, consisting of methotrexate, cyclosporine, antithymocyte globulin, or tacrolimus either alone or with different combinations for graft-versus-host disease (GVHD) prophylaxis (Table 2).

Table 1
Characteristics of Patients and Donors

Characteristic	Value
Age, yr	
Patients	8 (3-16)
Donors	2 (0.5-6)
Sex (female/male)	
Patients	23/29
Donors	28/26
Weight, kg	
Patients	24.5 (12-52)
Donors	13.1 (7.5-19)
Diagnosis	
TM, Pesaro low risk	36
TM, Pesaro high risk	6
Acute lymphoblastic leukemia	2
Acute myeloid leukemia	2
Wiskott-Aldrich syndrome	2
Juvenile myelomonocytic leukemia	1
Fanconi aplastic anemia	1
Sickle cell disease	1
Adrenoleukodystrophy	1

RESULTS

Transplantation Outcomes

In 49 of the 52 patients, full engraftment was achieved after first transplantation, with a mean value of total 4.6 (range, .6 to 14.8) $\times 10^6$ $CD34^+$ cells per kg of recipient weight. Three of the patients, all with TM (1 was assigned to high risk status and the others were assigned to low risk), failed to achieve engraftment. One of these patients underwent a second HSCT from the same donor, 1.5 years after the first transplantation, and full engraftment was achieved. Including this patient, full engraftment was achieved in 50 of 52 patients. HSCT outcomes are shown in Table 3. Among all patients, 1 patient developed grade IV, 1 patient developed grade II, and 2 patients developed grade I acute GVHD. Resolution was achieved in all patients with first-line treatments. None of the patients developed chronic GVHD or secondary graft failure. All 52 patients are alive and all, except the 2 with primary graft failure, are primary disease free without any complications. Forty-four patients are with full donor chimerism. Two of these patients have undergone transplantation from both of their twin siblings. They achieved full donor type chimerism and there was not predominance of cells from 1 twin. Eight patients, all with TM, achieved mixed chimerism but are transfusion independent.

PGD/HLA Typing Process and Total Costs

The median maternal age on the first IVF cycle was 32 years (range, 22 to 39 years). The median number of the IVF cycles to result with the birth of the donor was 2 (range, 1 to 8). Median time from the beginning of the first cycle to transplantation was 3.5 (range, 2 to 9) years. Median costs of the PGD/HLA typing and stem cell transplantation were €8500 (range, €1600 to €60,000) (US median, $9042; range $1702 to $63,826) and €44,000 (range, €35,000 to €60,000) (US median, $46,805; range, $37,232 to $63,826), respectively. The median total cost was €44,500 (range, €37,000 to €110,000) (US median, $44,347; range, $39,359 to $117, 014) (Table 4).